NSABP Biostatistial Center

National Surgical Adjuvant Breast and Bowel Project

Statistics Section
One Sterling Plaza
201 North Craig Street, Suite 350
Pittsburgh, Pennsylvania 15213

Phone: 412-383-2076
Fax: 412-383-1387

February 13, 2002

To: Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville MD 20852

From: John Bryant, Ph.D.
Director, NSABP Biostatistical Center

The enclosed comments apply to Docket No. 01D-0489, Draft "**Guidance for Clinical Trial Sponsors On the Establishment and Operation of Clinical Trial Data Monitoring Committees.**" These comments reflect the position of the Group Statisticians of the NCI-funded Cooperative Groups:

John Bryant Ph.D., National Surgical Breast and Bowel Project
John Blessing Ph.D., Gynecologic Oncology Group
Brent Blumenstein Ph.D., American College of Surgeons Oncology Group
John Crowley Ph.D., Southwest Oncology Group
Constantine Gatsonis Ph.D., American College of Radiology Imaging Network
Richard D. Gelber Ph.D., International Breast Cancer Study Group
Steven George Ph.D., Cancer and Leukemia Group B
Robert Gray Ph.D., Eastern Cooperative Oncology Group
Mark Krailo Ph.D., Children's Oncology Group
Thomas Pajak Ph.D., Radiation Therapy Oncology Group
Daniel Sargent Ph.D., North Central Cancer Treatment Group
Richard Sylvester Sc.D., European Organisation for Research and Treatment of Cancer
Dongsheng Tu Ph.D., National Cancer Institute of Canada Clinical Trials Group

These comments were also submitted via e-mail on 2/12/02. Please contact me at 412-383-2554 or bryant@nsabp.pitt.edu if you require any additional information.

01D-0489

C 10

FDA Draft Guidance for Clinical Trial Sponsors –
"On the Establishment and Operation of Clinical Trial Data Monitoring Committees" (http://www.fda.gov/cber/gdlns/clindatmon.htm)

Comments of the
Group Statisticians of the NCI-Funded
Cooperative Groups

Executive Summary

Cooperative Groups funded by the National Cancer Institute (NCI) enrolled about 26,000 patients to cancer treatment clinical trials in 2001, and also conduct large-scale cancer prevention trials. Application of the FDA Draft Guidance to these trials will have substantial negative effects not only in terms of cost and efficiency, but most importantly on patient safety. Specifically:

1) Blinding the study team to adverse event data will adversely affect patient safety. While the Data Monitoring Committee (DMC) should have important responsibilities for review, oversight and recommendation, primary responsibility for monitoring and reviewing toxicity data appropriately rests with the study leadership and the Group's Biostatistical Center.

2) Requiring independence of the statistician who prepares the DMC report is impractical in the Group setting. It will lead to miscommunications and misinterpretation of data, particularly if the closed meetings of the DMC were to exclude all persons who might have an intimate understanding of Group processes.

3) We are concerned about the practicability of requiring DMC approval for aspects of protocol design, such as the choice of a statistical interim monitoring rule. NCI-funded trials have already undergone exhaustive review at multiple levels prior to initiation. Any subsequent changes would require protocol amendments resulting in substantial delays in implementation.

The stated goals of the FDA Draft Guidance are being achieved by procedures already implemented by the Cooperative Groups. The current NCI Cooperative Group Data Monitoring Committee Policy was formulated to meet the unique requirements of the Cooperative Group setting, and has proven to work well in practice. It provides appropriate controls to assure both patient safety and the scientific integrity of the research. **We urge the FDA to specifically endorse the current NCI Cooperative Group DMC Policy for clinical trials conducted by the NCI-funded Cancer Cooperative Groups.**

Our comments specifically address the impact of the Draft Guidance on the NCI-sponsored Cooperative Group Program, and may or may not be relevant in other contexts, e.g. industry-sponsored trials.

1.0 Introduction

The National Cancer Institute (NCI) provides funding to various Cooperative Groups to design, conduct and analyze multi-center clinical trials consistent with national priorities for cancer treatment research[1]. Emphasis is placed on definitive, randomized Phase III studies and the developmental efforts preliminary to them. Approximately 26,000 patients were accrued to Group treatment studies last year, with many times that number in active follow-up. The Cooperative Groups are also involved in the design, conduct and analysis of cancer prevention trials involving tens of thousands of participants.

While the stated purpose of the FDA Draft Guidance is to discuss the roles, responsibilities and operating procedures of Data Monitoring Committees (DMCs) in settings where investigational products are being evaluated for possible marketing approval, this Guidance will nevertheless have a significant impact on the conduct of NCI-sponsored trials. This is because a large number of such trials involve investigational new agents and potentially form the basis for eventual registration efforts. **We are concerned that several aspects of the proposed Guidance have the potential to significantly degrade the quality, the efficiency, and even the safety of Cooperative Group trials.** Our comments specifically address the impact of the Draft Guidance on the NCI-sponsored Cooperative Group Program, and may or may not be relevant in other contexts, e.g. industry-sponsored trials.

The current NCI Cooperative Group DMC Policy (Smith et. al., 1997) has been in place since 1996. The NCI Policy and the FDA Draft Guidance differ in several important respects, and these differences should be critically examined, since there appears to be consensus within both NCI and the Cooperative Groups that the NCI Policy has worked well since its inception.

2.0 Preliminary Comments

Two observations are relevant to the discussion to follow:

2.1 **Definition of "Sponsor"**: In Section 1, the Draft Guidance adopts a very wide definition of this term: ***"In this document, references to the sponsor with regard to trial management and decision-making should be understood to refer also to any individual or group to which the sponsor has delegated the relevant management responsibilities."*** This definition clearly identifies the Cooperative

[1] The NCI-funded Cooperative Groups include the American College of Surgeons Oncology Group (ACoSOG); the American College of Radiology Imaging Network (ACRIN); the Cancer and Leukemia Group B (CALGB); the Children's Oncology Group (COG); the Eastern Cooperative Oncology Group (ECOG); the European Organisation for Research and Treatment of Cancer (EORTC); the Gynecologic Oncology Group (GOG); the International Breast Cancer Study Group (IBCSG); the National Cancer Institute of Canada Clinical Trials Group (NCIC); the National Surgical Adjuvant Breast and Bowel Project (NSABP); the North Central Cancer Treatment Group (NCCTG); the Radiation Therapy Oncology Group (RTOG); and the Southwest Oncology Group (SWOG).

Group and its Biostatistical/Data Management Center as a sponsor in any trial which it conducts, in addition to the NCI itself and to the pharmaceutical company that may provide drug and/or ancillary funding for the trial, and that would have primary interest in the trial for potential subsequent product registration. These three entities have very different roles, obligations and perspectives. It is our view that failure to consider these distinctions may have led to recommendations that may prohibit the Cooperative Groups and their Biostatistical Centers from assuming responsibilities and functions that are most appropriately assigned to them, and that are essential to the success of the trial.

2.2 The Draft Guidance makes no real distinction between industry and government sponsorship: In Section 1.2 it is stated that ***"FDA believes that the issues discussed in this document arise in both industry- and government-sponsored trials, and therefore has not differentiated between them. We recognize that the potential conflicts of interest faced by government sponsors are somewhat different from those of industry sponsors, so that the implications for the approach to monitoring, particularly with regard to confidentiality and independence issues, may also differ to some extent."*** Unfortunately these differences and their implications are never clarified, so the reader is left to guess when recommendations should or should not apply in the Cooperative Group Setting.

3.0 Monitoring Toxicity and Adverse Events

Although the Draft Guidance is somewhat obscure on this point, in several places it appears to imply that the study leadership (Steering Committee), and even the trial statistician should have essentially no role in ongoing toxicity monitoring, and in fact should be blinded to toxicity and adverse event data except as aggregated over study arms. This appears to be recommended even in cases where the trials themselves are not double-blinded, as is the case in most cancer therapy trials. Comments at the public hearing held 11/27/01 in Bethesda MD also appeared to reinforce this impression. Several statements to this effect which appear in the draft Guidance are summarized below:

- Section 3.2 (Responsibilities of the Steering Committee): ***"A Steering Committee ... has primary responsibility for designing the study, maintaining the quality of study conduct, and writing the final study report."*** Note the complete absence of <u>any</u> role in review of ongoing toxicity data. It seems clear that the intent of the Draft Guidance is that the DMC is to have primary or even exclusive responsibility for ongoing monitoring of toxicities and adverse events.

- Section 4.2 (Confidentiality of Interim Data): ***"Any part of the interim report to the DMC that includes comparative effectiveness <u>and safety data</u> presented by study group, whether coded or uncoded, should generally be available only to***

DMC members during the course of the trial, including any follow-up period, that is until the blind is broken."

- Section 4.3.1.2 (In the discussion of appropriate topics for open sessions)*:* ***"These nonconfidential items may include, for example, status of recruitment, baseline characteristics, ineligibility rate, status of data submissions and quality, aggregated safety data, aggregated outcome data."***

- Section 4.4: "*...**responsibility [for detailed review of SAEs] generally rests with the sponsor, who reviews such events promptly, usually blinded to study arm assignment, and who has responsibility of reporting serious, unexpected adverse events to FDA under 21 CFR 312.32."***

- Section 6.3 (Risks of Exposure to Interim Data): ***"One concern is that unblinding of the sponsor increases the risk of further unblinding, e.g. of ... investigators, thereby potentially compromising objective safety monitoring ..."***

Our position is that **for reasons of patient safety the assignment of primary responsibility for monitoring toxicity and adverse events must rest with the study leadership and the Cooperative Group.** While we would never suggest that DMC members are not competent to perform such a task given appropriate resources and time, it is completely unrealistic to expect that even the most competent committee could successfully undertake this task in the Cooperative Group setting. The Phase III treatment trials of each Group are typically monitored by a single DMC, which meets twice yearly, and which might also convene by conference call from time to time as needs dictate. Each such Committee is responsible for monitoring from 10 to 30 large, multi-center trials in a variety of diseases. Adequate real-time adverse event monitoring of these trials requires the type of infrastructure developed by the Cooperative Groups for just such purpose, and delegation of this task to the DMCs as currently constituted would be an unacceptable abdication of responsibility. Further, it is unreasonable to expect that sufficient numbers of individuals with appropriate expertise could be recruited to serve on DMCs in order to make such an approach feasible. It is for these reasons that the NCI Policy on DMCs appropriately assigns primary responsibility for the review of toxicity data to the study leadership, although the DMC is assigned important responsibilities for review, oversight and recommendation.

Further, it is unlikely that blinding the study leadership to comparative toxicity and adverse event data accomplishes anything. In trials that are not double-blinded, the Cooperative Groups have for years provided their investigators with Progress Reports and Meeting Books with comparative toxicity data. Similar data are provided to IRBs to assist them in annual review of ongoing protocols. To our knowledge this has not adversely effected equipoise or jeopardized the trials in any material way.
A rationale given in the Draft Guidance for blinding the study leadership to interim results is that if such reports are shared, it may become impossible for the sponsor to make potentially warranted changes in the trial design or analysis plan in an unbiased manner. When applied to toxicity or adverse event data, this argument is not persuasive,

except possibly in a very special case of a double-blinded trial where these endpoints were primary, and where safety concerns were very minimal. In virtually all cancer treatment trials, this is not the case: Survival, relapse-free or progression-free survival, or response rates are the endpoints of primary interest, and generally formal, precise statistical comparisons of toxicities across arms is of little importance. In these cases, blinding the study leadership to comparative toxicity data could be theoretically justified only by implausible assumptions of extreme correlation between toxicity and outcome.

Perhaps our reading of the Draft Guidance is in error, and in fact there is agreement with the NCI DMC Policy that, at least in the Cooperative Group setting, primary responsibility for ongoing toxicity and adverse event monitoring rests with the study leadership and the Cooperative Group, with review and oversight provided by the DMC. If so, we urge that this position be clarified in the document. Otherwise, we must strongly disagree with the position taken in the Draft Guidance on this matter.

4.0 Independence of the Statistician Who Prepares Interim Reports

In Section 4.2 of the Draft Guidance, the argument is made that interim data will be best protected from inappropriate access if it is prepared for analysis by an entity independent of the sponsor and its investigators. In particular, ***"The statistician preparing reports to the DMC should ideally be independent of the sponsor and clinical investigators (and steering committee if there is one) to avoid inadvertent influence of data trends on the conduct of the trial."*** This recommendation again is a departure from the NCI DMC policy, which specifies that the interim reports should be prepared by the study statistician.

The case to be made for the FDA Draft Guidance position is much less strong in the Cooperative Group setting than in the industrial setting, a point to which we will return below. However, before doing so it should first be pointed out that, in the Cooperative Group setting, it will not be practical to arrange for statisticians independent of the Cooperative Groups to prepare and present interim reports for each of the hundreds of Phase III trials conducted under NCI auspices each year. There are simply not enough qualified personnel available to do so, nor are funds available in the Cooperative Group budgets to retain them if they were available. Even more importantly, the potential for miscommunication and misinterpretation of data is overwhelming; particularly if the closed meetings of the DMC were to exclude all personnel who might have an intimate understanding of Group processes, significant errors are likely to occur.

Most of the Cooperative Groups have for many years contributed to meta-analysis projects such as the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). In these collaborations, elaborate precautions are taken to ensure that data are compiled, transferred and summarized without error. These precautions involve considerable back-and-forth communication between the Trialists and the Cooperative Groups, are quite time consuming, and would be difficult to carry out in a truly blinded fashion. Despite

working with some of the most competent researchers in the world, errors sometimes do occur and are not caught until data presentation in working group meetings. Given this experience, it is hard to believe that the recommendation of the Draft Guidance could be practically implemented in the Cooperative Group Setting without substantial cost in terms of time, money, and accuracy of study results that would grossly outweigh any utility the recommendation might afford.

The case to be made for independent analysis loses credibility in the Cooperative Group setting. In particular, the Cooperative Group statistician is presumably free from financial conflict of interest and is generally rather autonomous from the remainder of the study leadership, both organizationally and by virtue of the protections of academic freedom and tenure. Further, the essential mission of the Cooperative Groups consists of the design and conduct of scientifically valid clinical trials. While it is theoretically true that knowledge of interim results could inappropriately impact the statistician's evaluation of proposed trial modifications, by training he or she is sufficiently aware of and sensitive to these issues. Therefore we believe that this is very rarely a practical concern.

It is also the case that for most adjuvant cancer treatment trials, relatively little efficacy data (in terms of patient deaths or treatment failures) has been obtained at the point in time when the trial's accrual goal has been met, or even at the point in time when all randomized treatment has been completed. In this case, little interim information could be brought to bear on any proposed trial changes (e.g. increased sample size, dropping a treatment arm, etc.). Any modifications of study endpoints or analysis methods made after closure of accrual will not be problematic as the Agency is free to request analyses of the original endpoints using the original methods, as it deems appropriate.

Finally, it should be acknowledged that protocol modifications of NCI-funded trials currently can not be made by the study leadership without extensive independent review. All proposed amendments must undergo evaluation and approval at CTEP; all major protocol modifications are, by NCI policy, subject to review and approval by the DMC; all amendments of a trial involving an investigational agent are subject to FDA review and comment; and Central IRB (CIRB) and individual IRB approvals are required. This series of competent reviewers makes it highly unlikely that an egregious misuse of interim data will render the results of a trial uninterpretable. While such a concern could conceivably arise at very infrequent intervals, the proposed remedy is far more dangerous and is inordinately costly.

5.0 Distinction Between Accrual and Follow-up Phases

The FDA Draft Guidance makes little or no distinction between trials for which patients are still being accrued and/or treated, and those for which all patients have been accrued and all randomized therapy has been given. In contrast, the NCI DMC Policy makes a sharp distinction: In the former case, efficacy results are considered strictly confidential and must not be divulged to any person outside the DMC; But under the NCI Policy, after the termination of all randomized treatment the DMC may at its discretion release

outcome data on a confidential basis to a specified group of investigators for purposes of planning new protocols. We feel the overall program of the Cooperative Groups is enhanced by this flexibility; without it, protocol development would be slower and less certain. We urge the drafters of the FDA Guidance to consider similar flexibility. For the reasons summarized above, the impact of any protocol amendments that take place following cessation of randomized treatment is "recoverable" in the sense that FDA could request an analysis based on the original protocol endpoints and methods.

6.0 Independence of the DMC

Under the NCI DMC Policy, DMCs may include Cooperative Group members, as long as a majority of the voting members are from outside the Group. The NCI Policy states that Cooperative Group members on the DMC should regard themselves as representing patient interests rather than Group interests; like all DMC members, they are required to keep all information confidential. Further, Group members can have no financial interests in the trials they monitor. Study Group members or Disease Committee leadership must recuse themselves from monitoring studies in which they are involved.

One advantage to this policy is practical: Given the large number of Cooperative Groups and Cooperative Group trials to be monitored, it is difficult to find qualified personnel who are willing to serve on DMCs without compensation. Permitting some Group members to participate on the Group DMC is very helpful in this regard. A second advantage is the enhanced familiarity of Group members with the Group's scientific agenda and methods, and the considerable breadth of expertise and experience they bring to the DMC. Given the special nature of the Cooperative Group as sponsor, such arrangements appear to us to be acceptable and indeed beneficial.

7.0 Role of the DMC in Protocol Approval

In Section 4.3.2, the Draft Guidance recommends that the DMC should review and approve the statistical interim monitoring plan for each study, prior to its initiation. This suggestion was expanded by several speakers at the 11/27/01 public hearing, who suggested further protocol review by the DMC (most notably, review and approval of informed consent). In the Cooperative Group setting, this would generally be unworkable, since NCI-funded trials will have already undergone several rounds of review and approval at CTEP, CIRB, FDA, etc. Any subsequent changes would necessitate protocol amendments that in turn would have to be reviewed and approved, thereby substantially delaying protocol initiation. In view of the fact that all aspects of the protocol are reviewed by competent agencies prior to start-up, it seems to us unwise to involve the already overburdened DMCs in this process as well.

8.0 Conclusions

Considering the issues discussed above, implementation of the Draft Guidance will have a substantial negative impact on the conduct of clinical trials by the NCI-funded Cancer Cooperative Groups. We believe that for these trials, the stated goals of the Draft Guidance are being achieved by procedures already implemented by the Cooperative Groups. We urge the FDA to endorse the current NCI Cooperative Group DMC Policy specifically for clinical trials conducted by the NCI-funded Cancer Cooperative Groups, both in the treatment and prevention settings.

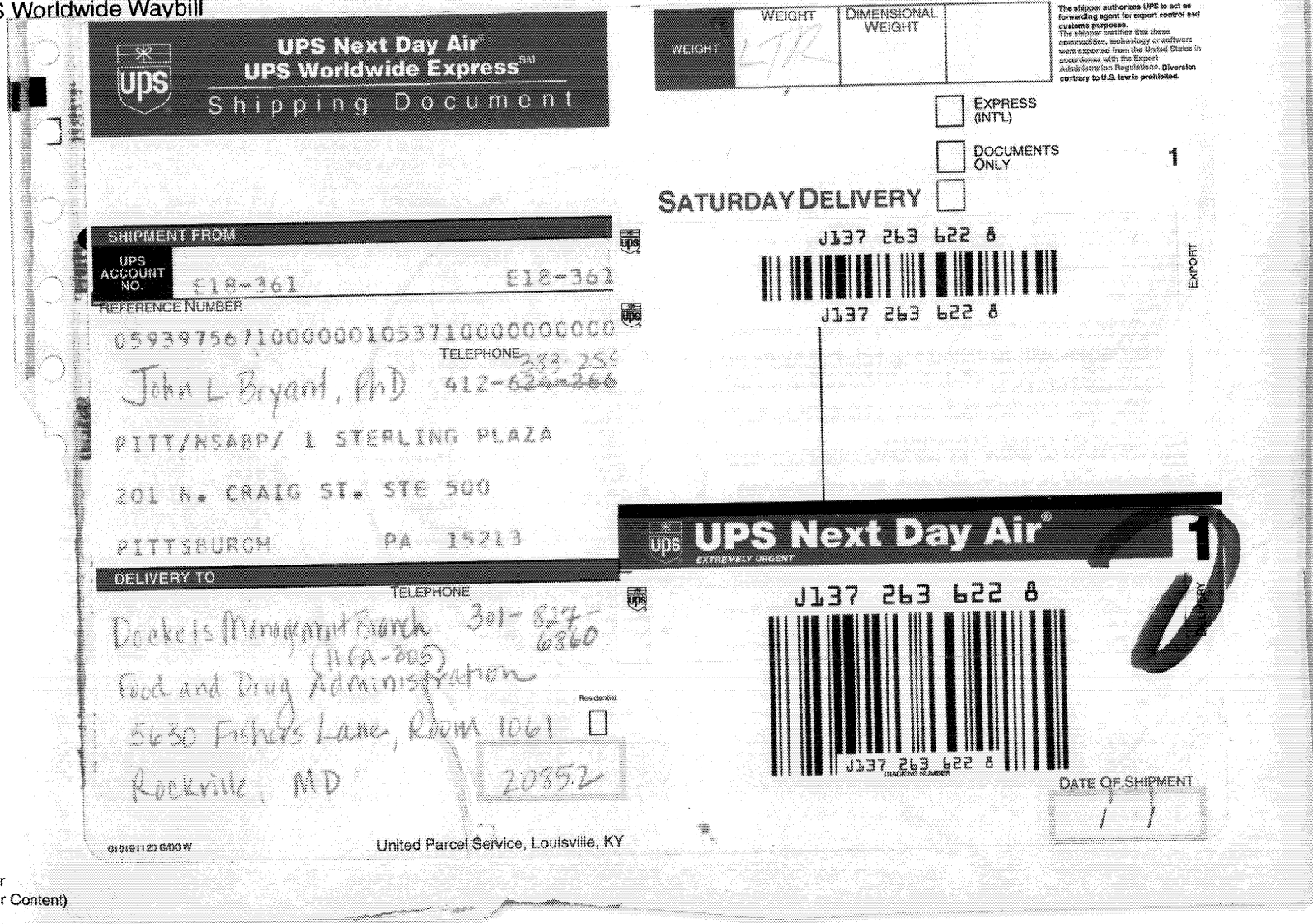
John Bryant Ph.D., National Surgical Breast and Bowel Project
John Blessing Ph.D., Gynecologic Oncology Group
Brent Blumenstein Ph.D., American College of Surgeons Oncology Group
John Crowley Ph.D., Southwest Oncology Group
Constantine Gatsonis Ph.D., American College of Radiology Imaging Network
Richard D. Gelber Ph.D., International Breast Cancer Study Group
Steven George Ph.D., Cancer and Leukemia Group B
Robert Gray Ph.D., Eastern Cooperative Oncology Group
Mark Krailo Ph.D., Children's Oncology Group
Thomas Pajak Ph.D., Radiation Therapy Oncology Group
Daniel Sargent Ph.D., North Central Cancer Treatment Group
Richard Sylvester Sc.D., European Organisation for Research and Treatment of Cancer
Dongsheng Tu Ph.D., National Cancer Institute of Canada Clinical Trials Group

Reference

Smith MA, Ungerleider RS, Korn EL, Rubinstein L, Simon R (1997), "Role of Independent Data-Monitoring Committees in Randomized Clinical Trials Sponsored by NCI." *J Clin Oncol* 15, 2736-2743

ls in This Space

- UPS Tracking Label and your address label
- UPS Air Shipping Document
- UPS Worldwide Waybill



led Fiber
onsumer Content)